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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,545	01/15/2004	Peter Fischer	SAN1002USC1	3057

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EXAMINER	
POLANSKY, GREGG	
ART UNIT	**PAPER NUMBER**
1609	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,545	FISCHER, PETER	
	Examiner	Art Unit	
	Gregg Polansky	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/15/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiners Response to Applicant Remarks

Applicant's Remarks, which accompanied the present application, have been considered but they are not persuasive (with one exception, as noted below). When the Applicant defines "non-anticholinergic" delirium as a "deliria which occur without anticholinergically acting substances being administered beforehand", it is assumed that Applicant is referring to those substances which are direct acetylcholine receptor antagonists (e.g., atropine, scopolamine, etc.). However, it has been shown that many drugs, which are not considered to be anticholinergic, may also reduce central cholinergic activity (*see* Rupreht et al). They teach that central anticholinergic syndrome (CAS) describes delirium manifested through a central cholinergic mechanism. This does not limit it to directly acting anticholinergic agents, but can include many agents and metabolic imbalances that have indirect effects on central cholinergic activity. For instance, ß-adrenergic and dopaminergic agonists, opiates, and barbiturates may hinder cholinergic neurotransmission through presynaptic inhibition of acetylcholine release (*see* Flacker, et al, page B240, column 1, lines 33-37). Pestronk et al postulate that the mechanism of action of lithium is through modifying acetylcholine receptor metabolism. It has been shown that hypoxia can affect cerebral acetylcholine synthesis (*see* Parikh et al, page 1224, column 2). Furthermore, Flacker et al (page B250, column 2, 1st paragraph) relates that acetylcholine production "is closely tied to the oxygen and glucose citric acid cycle", and that "hypoglycemia, in experimental animals, depresses acetylcholine synthesis...". Indeed, Rupreht, et al, state that a

diagnosis of CAS is made through a positive therapeutic response to physostigmine. In other words, if physostigmine has a positive effect on CAS symptoms, then the diagnosis **is** CAS. Applicant states that the teachings of Rupreht et al do "not apply to postoperative delirium which develops after a 'lucid period of duration'...which is the focus of the pending application". This definition does not appear anywhere in the claims or specifications of the instant invention. Furthermore, Applicant states in the specifications " this invention relates therefore to treatment of acute states of confusion **of any type**".

Therefore, Rupreht et al teaching of an anticholinesterase treatment of central anticholinergic syndrome (CAS) includes the non-anticholinergic delirium taught in the instant invention and is not limited, as Applicant asserts, to deliria caused by anticholinergic drugs.

Enz teaches the use of rivastigmine (a phenyl carbamate acetylcholinesterase inhibitor) for the treatment of various neurological conditions (including acute confusion disorders (delirium)) that have been shown by others to respond to acetylcholinesterase inhibitors. He does not restrict the treatment to conditions that are caused by anticholinergic drug intoxication or degeneration of the cholinergic system, nor does he exclude the treatment of deliria of non-anticholinergic etiology. This is contrary to the assertion by Applicant that Enz does not anticipate the instant invention.

The Examiner agrees with the Applicant's assertion that Oshiro et al teach a disturbance-of-consciousness that is different from that of the instant application. Therefore reference to Oshiro et al has been removed from this Office Action.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 7-10 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Rupreht et al (pages 295-304). Claims 7 and 8 are drawn to the method of treating a non-anticholinergic state of delirium in a patient in need thereof, through the use of acetylcholinesterase inhibitors. Claims 9, 10, and 13 are drawn to the method of treating non-anticholinergic delirium, which is a postoperative delirium or, caused by an internal disease or a hypoglycemic process, through the use of acetylcholinesterase inhibitors. Rupreht et al teach the central anticholinergic syndrome (CAS), which include confusion or delirium occurring during the postoperative period, and caused by overdoses of both anticholinergic medication (e.g., atropine) and non-anticholinergic medication (e.g. opioids, halothane, benzodiazepine, anesthetics, hypoxia and hypoglycemia). Rupreht further teaches that CAS occurs when central cholinergic sites are occupied by specific drugs and also as a result of an insufficient release of acetylcholine (as can be caused by non-anticholinergic drugs; see translation, page 2, 1st paragraph), and can be effectively treated by a therapeutically effective acetylcholinesterase inhibitors, including, physostigmine, galantamine, tacrine.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rupreht, et al alone. Rupreht et al's teachings are mentioned in 102 rejection (supra). Claims 11 and 12 are drawn to the method of treating delirium caused by hypoglycemic coma and resuscitation of a patient, respectively, through the use of and acetylcholinesterase inhibitor. Even though Rupreht et al does not mentioned hypoglycemic coma or resuscitation as the causative factor for delirium, it would have been obvious to one of ordinary skill in the art at the time of invention to extend Rupreht et al's teaching of acetylcholinesterase inhibitor administration for treating delirium or confusion caused by hypoglycemia, hypoxia and neurological damage resulting from surgery, to delirium caused by hypoglycemic coma and resuscitation. One would have motivated to do so, with reasonable expectation of success, because Rupreht's teaching (i.e., acetylcholinesterase inhibitor treatment) includes hypoglycemia which encompasses hypoglycemic coma and neurological damages or hypoxia where it is well known in the art that improper resuscitation often causes neurological damages or hypoxia, absent evidence to the contrary.

Claims 7-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Enz (US 5,602,176) in view of Flacker et al, Parikh et al, Rupreht et al and Pestronk et al. Claim 14 is drawn to the method of treating delirium through the use of rivastigmine. Enz teaches a method of treating acute confusion disorders using a pharmaceutical composition comprising a therapeutically effective amount of (s)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl carbamate (rivastigmine: chemical name, used hereafter);see column 5, lines 1-3. Enz also teaches that rivastigmine is acetylcholinesterase inhibitor; see column 1. It also noted that the term "delirium" is a synonym of "acute confusion disorder" as admitted in instant application; see instant specification at page 4, second paragraph (lines 30-32).

However Enz is silent about the etiologies (causative factors) of acute confusion disorder (delirium). Flacker et al and Rupreht et al teach a central cholinergic etiology for delirium (see Rupreht et al abstract and Flacker et al page B239, column 2, last paragraph). Parikh et al teach of a central cholinergic mechanism of postoperative delirium (page 1224, subparagraph 'Pathophysiology'). Furthermore, all teach hypoxia, hypoglycemia, and other "non-anticholinergic" effects on central cholinergic activity (decreased) and production of delirium. Parikh et al also teach of delirium caused by "internal disease" (e.g., page 1226, column 1, lines 10-25).

It would have been obvious to one of ordinary skill in the art at the time of the invention to select cholinergic CNS effectors (i.e. acetylcholinesterase inhibitor (e.g., rivastigmine)) suggested by Enz, to treat delirium (acute confusion disorder), of both anticholinergic and non-anticholinergic etiologies, because both Flacker et al and

Rupreht et al teach a correlation between decreased central cholinergic activity and delirium and that the decreased central cholinergic activity could be caused by cholinergic and non-anticholinergic factors, such as substance poisoning (equivalent term with intoxication), non-anticholinergic drugs, endogenous anticholinergic substances, hypoglycemia, hypoxia, and metabolic disorders.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Janowsky et al and Pestronk et al in view of Flacker et al, Parikh and Rupreht. Claim 16 is drawn to a method of treating delirium caused by non-anticholinergic intoxication through the use of and acetylcholinesterase inhibitor. Janowsky et al (see abstract) demonstrate that lithium antagonizes central cholinergic activity. Pestronk et al (see abstract), through their examination of acetylcholine metabolism in skeletal muscle, postulate that the mechanism of action of lithium is through modifying the number of acetylcholine receptors (i.e., reduction of the number of acetylcholine receptors).

It would be obvious to one skilled in the art to postulate a similar effect of lithium at CNS acetylcholine receptors. Flacker et al, Parikh et al, and Rupreht et al teach an anticholinergic mechanism for deliria and its effective treatment with cholinesterase inhibitors. It would be obvious to one skilled in the art that delirium caused by lithium intoxication might be through a lithium-induced decrease in central cholinergic activity. One would be motivated to combine these teachings of a lithium-induced decrease in central cholinergic activity with the teachings of a central cholinergic mechanism in deliria and its effective treatment with acetylcholinesterase inhibitors, to find a treatment for lithium-induced deliria.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. in view of Rupreht et al. Claim 15 is drawn to the method of treating delirium caused by non-anticholinergic substance withdrawal. Fisher et al (Column 5, Lines 39-59) teach the use of a central muscarinic (acetylcholine) agonist in the treatment of conditions which may be caused by central cholinergic hypofunction. They go on to teach that these conditions include acute confusion and alcohol withdrawal ("non-anticholinergic substance withdrawal"). Rupreht et al teach the role of the central cholinergic system in delirium and of the use of acetylcholinesterase inhibitors in the treatment thereof. Since acetylcholinesterase inhibitors act by increasing the amount of acetylcholine in the cholinergic CNS (and thus increase cholinergic activity) and a cholinergic agonist also results in increased activity of cholinergic neurons, it would be obvious to one of ordinary skill in the art to combine these teachings.

One would have been motivated to treat non-anticholinergic delirium by administering effectors of cholinergic CNS, with reasonable expectation of success, because deactivation of the cholinergic nervous system is the biological mechanism for inducing delirium wherein cholinergic CNS effectors (e.g. acetylcholinesterase inhibitors or acetylcholinergic receptor agonists) effectively and directly activates the cholinergic nervous system and improves the delirium (acute confusion disorder) as suggested by each cited reference.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same or

similar) ingredients and share common utilities, and pertinent to the problem which applicant is concerning. MPEP 2141.01(a).

Conclusion

4. The claims 7-16 are rejected.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571) 272-9070. The examiner can normally be reached on M-F 7:30 A.M. - 5:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gregg Polansky

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